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Factors associated with serum high mobility group box 1 (HMGB1) levels in a general population

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Abstract

High mobility group box 1 (HMGB1), a nonhistone chromatin-associated protein, is implicated as a mediator of both infectious and non-infectious inflammatory conditions. Clinical research on this protein in humans just has begun; serum HMGB1 was reported to be elevated in a small number of critically ill patients suffering from sepsis. However, the kinetics, distribution and factors associated with circulating HMGB1 are unknown in a general population. In this study, we examined these issues in a large population of healthy subjects. Fasting blood samples were obtained from 626 subjects (237 males and 389 females). HMGB1 levels showed a skewed distribution with a mean of 1.65 ± 0.04 ng/ml. Multiple stepwise regression analyses found that white blood cell (WBC) counts ($P = .016$) and the soluble form of receptor for advanced glycation end products (sRAGE; $P < .001$, inversely), which is also known to be a receptor for HMGB1, were independently associated with HMGB1 levels. We demonstrated for the first time that circulating HMGB1 levels were inversely associated with sRAGE levels in a general population. Because RAGE is involved in HMGB1 signaling, our present study suggests that sRAGE may capture and eliminate circulating HMGB1 in humans.

1. Introduction

High mobility group box-1 (HMGB1) was first isolated from perinatal rat brain in 1987 as a heparin-binding protein that could promote neurite outgrowth in central neurons [1]. It was originally described as a DNA-binding nonhistone chromosomal protein that had been implicated in diverse cellular functions such as stabilization of nucleosomal structure and regulation of transcriptional factors [2]. Recently, HMGB1 has been implicated as a putative danger signal involved in the pathogenesis of a variety of inflammatory conditions [3]. HMGB1 is not only released passively from necrotic cells, but is also secreted actively by immune cells such as monocytes, macrophages and dendritic cells, thus participating in various inflammatory processes, including maturation of immune cells, release of cytokines and other inflammatory mediators, and tissue remodeling [4,5]. Neutralizing antibodies raised against HMGB1 or HMGB1 antagonists were reported to improve survival in severe endotoxemia and sepsis, ameliorate experimental autoimmune arthritis, and decrease tumor incidence and size [6-9]. In humans, serum levels of HMGB1 are increased in several inflammatory diseases such as infection, sepsis and septic shock [10,11], acute coronary syndrome [12,13], and disseminated intravascular coagulation [14].

The receptor for advanced glycation end products (RAGE) is thought to be one of the important receptors mediating HMGB1 signaling [15-17]. The HMGB1-RAGE interaction promotes chemotaxis and maturation of immune cells, enhances the expression of adhesion molecules in endothelial cells, and stimulates the production of cytokines

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by various types of cells [17-19]. Recently, a soluble form of RAGE (sRAGE) was identified in the circulation [20]. Since administration of a recombinant sRAGE has been shown to block the inflammatory reactions in various experimental models [16,17,21,22], it is considered that sRAGE may capture and eliminate circulating HMGB1 and may be one of the determinants of circulating HMGB1 levels. Thus serum HMGB1 levels could be regulated by many factors. However, it remains unclear how serum HMGB1 levels are regulated in humans in the absence of active inflammation. Accordingly, in this study, we examined factors associated with serum HMGB1 levels in a large and apparently healthy general population. We found that white blood cell (WBC) counts are positively and sRAGE levels are inversely correlated with serum HMGB1 levels.

2. Methods

2.1. Study subjects

We have been conducting annual health check-ups of residents over 40 years old in a small fishing community in southwestern Japan (Uku town) since 2002. This town is an isolated island in a part of Sasebo city in Nagasaki prefecture. These check-ups include a review of medical history, routine physical examination, routine blood chemistry tests, ECG, echocardiography, and carotid artery ultrasonography. From 2004 to 2006, a total of 640 residents (241 males and 399 females, mean age: 65.8 ± 9.7 years) received these health check-ups. During these 3 consecutive years, we investigated factors associated with serum HMGB1 levels. We excluded 14 subjects with apparent active inflammatory disorders, cardiovascular disease, and cancers, or subjects who rejected the blood test. In the end, complete data sets were available for 626 subjects (237 males and 389 females).

2.2. Data collection

The subjects' medical history, smoking habits and, use of alcohol were ascertained by questionnaire. Height and weight were measured, and body mass index (BMI) (kilograms per meter squared) was calculated as an index of the presence or absence of obesity. Waist circumference was measured at the level of the umbilicus in the standing position. Blood pressure (BP) was measured twice, first in a sitting position and then in a supine position after a 3-minute interval, using an upright standard sphygmomanometer. Vigorous physical activity and smoking were avoided for at least 30 minutes before BP measurement. The fifth phase diastolic pressure measurement in the supine position was used for analysis.

Blood was drawn from the antecubital vein in the morning after overnight fasting for determinations of lipids [total cholesterol, high-density lipoprotein cholesterol (HDL-c), low-density cholesterol (LDL-c)], fasting plasma glucose (FPG), HbA_{1c}, insulin, blood urea nitrogen (BUN), creatinine, uric acid, and high-sensitive C-reactive protein (hs-CRP). These chemistries were measured at a commercially available laboratory (The Kyodo Igaku Laboratory, Fukuoka, Japan). In addition, blood was drawn for examination of serum levels of HMGB1 and sRAGE, which were measured using enzyme-linked immunosorbent assay kits according to the suppliers' recommendations (SHINO-TEST, Tokyo, Japan and R&D Systems, Minneapolis, MN, respectively). Glomerular filtration rate (GFR) was estimated using the Modification of Diet in Renal Disease (MDRD) study equation modified with a Japanese coefficient [23]. The study was approved by the mayor and the welfare department of Uku town, as well as by the Ethics Committee of Kurume University. All participants gave written informed consent.

2.3. Statistical methods

First, we examined the distributions of WBC counts, triglycerides, estimated GFR, insulin, hs-CRP, sRAGE, and HMGB1. Because of their skewed distributions, natural logarithmic (ln) transformations were performed. Mean value, and upper and lower 95% confidence intervals (CI) were exponentiated and presented as geometric means ± standard deviation (SD), where SD was approximated as the difference of the exponentiated CI divided by 3.92, which is the SD in a 95% CI where data are normally distributed. Medications for hypertension, hyperlipidemia and diabetes were coded as dummy variables. Multivariable analysis after adjustments for age and sex was performed for correlates of serum HMGB1 levels. To determine independent correlates of serum HMGB1 levels, multiple stepwise linear regression analysis was performed. Mean levels of serum HMGB1 stratified by the independent correlates were then compared using analysis of covariance (ANCOVA), adjusted for age and sex as covariates. Statistical significance was defined as $P < .05$. All statistical analyses were performed with the use of the SAS system (SAS Institute, Cary, NC).

3. Results

Demographic data for the 626 subjects are presented in Table 1. Mean serum levels of HMGB1 were 1.69 ± 0.04 ng/ml in males and 1.62 ± 0.04 ng/ml in females. Fig. 1 shows distributions of HMGB1 levels. HMGB1 distributions were skewed in both males and females. Table 2 shows the results of multivariable analysis for factors correlated with serum HMGB1 levels. Parameters significantly associated with HMGB1 levels were WBC counts ($P = .016$), hs-CRP ($P = .029$), and sRAGE ($P < .001$, inversely). Because these parameters could be closely correlated, multiple stepwise regression analysis was performed. This analysis showed that sRAGE ($P < .001$, inversely) and WBC counts ($P = .016$) were independently related to HMGB1 levels ($R^2 = 0.034$) (Table 3).

Table 1
Demographics of study subjects

Characteristics	Male (n = 241)	Female (n = 399)	Total (N = 640)
Age (year)	67.3 ± 8.4	64.9 ± 10.3	65.8 ± 9.7
Body mass index (kg/m^2)	23.6 ± 3.1	23.7 ± 3.5	23.6 ± 3.3
Waist circumference (cm)	86.0 ± 7.7	82.4 ± 9.9	83.7 ± 9.3
Systolic blood pressure (mmHg)	137.1 ± 19.9	139.6 ± 20.6	138.7 ± 20.3
Diastolic blood pressure (mmHg)	81.3 ± 11.0	79.6 ± 11.5	80.3 ± 11.4
Ankle brachial pressure index	1.1 ± 0.2	1.0 ± 0.2	1.0 ± 0.2
White blood cell counts (/μl)[a]	5584.8 ± 145.3	5157.6 ± 134.2	5315.4 ± 138.3
HMGB1 (ng/ml)[a]	1.69 ± 0.04	1.62 ± 0.04	1.65 ± 0.04
Total cholesterol (mg/dl)	200.5 ± 36.5	210.9 ± 36.0	207.0 ± 36.5
HDL- cholesterol (mg/dl)	54.7 ± 14.4	60.8 ± 14.1	58.4 ± 14.6
Triglycerides (mg/dl)[a]	97.2 ± 2.5	85.6 ± 2.2	89.8 ± 2.3
LDL- cholesterol (mg/dl)	121.0 ± 33.1	127.9 ± 32.6	125.3 ± 32.9
BUN (mg/dl)	19.9 ± 5.3	17.4 ± 4.8	18.3 ± 5.1
Creatinine (mg/dl)	0.8 ± 0.2	0.6 ± 0.1	0.7 ± 0.2
Estimated GFR (ml/min/1.73m^2)[a]	74.5 ± 1.9	74.1 ± 1.9	74.3 ± 1.9
Uric acid (mg/dl)	6.0 ± 1.3	4.7 ± 1.2	5.2 ± 1.4
Hemoglobin A1c (%)	5.4 ± 0.7	5.3 ± 0.4	5.3 ± 0.5
Insulin (μU/ml)[a]	4.4 ± 0.1	4.1 ± 0.1	4.2 ± 0.1
hs CRP (mg/dl)[a]	0.06 ± 0.002	0.04 ± 0.001	0.04 ± 0.001
sRAGE (ng/ml)[a]	0.43 ± 0.01	0.46 ± 0.01	0.45 ± 0.01
Smoking (%, yes)	18.7	1.5	8.0
Alcohol (%, yes)	58.5	9.0	27.6
Medications for			
Hypertension (%, yes)	42.3	36.8	38.9
Hyperlipidemia (%, yes)	11.2	14.3	13.1
Diabetes (%, yes)	10.0	3.0	5.6

Data are means ± standard deviation or percentage, unless otherwise indicated.
Abbreviations: HMGB1, high mobility group box 1; HDL, high density lipoprotein; LDL, low density lipoprotein; BUN, blood urea nitrogen; GFR, glomerular filtration rate; hsCRP, high sensitive C reactive protein; sRAGE, soluble receptor for advanced glycation end products.
[a] Log-transformed values were used for the calculation and reconverted to anti-logarithm forms.

In order to further examine the association between serum HMGB1 and WBC counts or sRAGE, we performed analysis of covariance. Fig. 2 shows the means levels of HMGB1 stratified by tertiles of WBC counts (upper panel) and sRAGE (lower panel) adjusted for age and sex. Serum HMGB1 levels showed dose-dependent relationships with both factors (P = .006 for WBC counts and P = .007 for sRAGE).

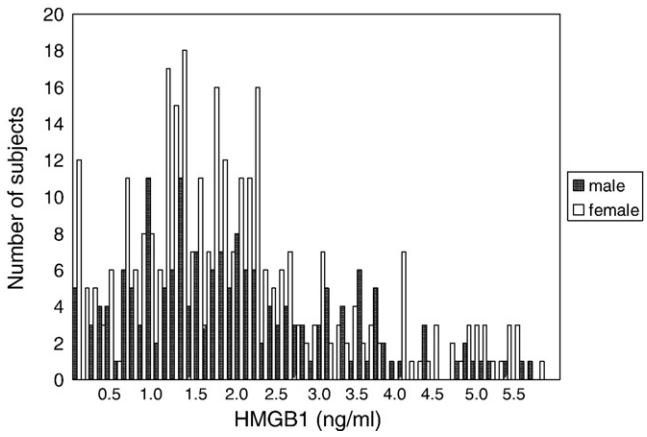

Fig. 1. Distributions of HMGB1 levels in males and females; distributions are skewed for both sexes.

4. Discussion

In the present study, we demonstrated for the first time that WBC counts (positively) and sRAGE levels (inversely) were independently associated with serum HMGB1 levels in an apparently healthy general population.

As far as we know, there have been no large-scale studies of serum HMGB1 levels either in patients or in healthy subjects. In this study, we found that HMGB1 distributions were skewed in both males and females. We also found that the mean serum levels of HMGB1 (1.65 ± 0.04 ng/ml) in our population were much lower than those reported in patients with infection, sepsis and septic shock [10,11], acute coronary syndromes [12,13], and disseminated intravascular coagulation [14]. The values in our population were similar to those of non-infected Danish patients (1.54 ng/ml) [10] and controls of other several studies [12,13]. Of course, we excluded any patients with apparent active inflammatory disorders, cancer and cardiovascular disease by careful review of medical history, ECG, and echocardiography. A recent study has indicated that, HMGB1 levels were

Table 2
Multivariable analysis for correlates of HMGB1 levels adjusted for age and sex

Characteristics	β	SE	*P*
Body mass index (kg/m^2)	-0.012	0.014	.387
Waist circumference (cm)	-0.002	0.005	.522
Systolic blood pressure (mmHg)	0.003	0.002	.283
Diastolic blood pressure (mmHg)	0.001	0.004	.865
White blood cell counts (/μl)[a]	0.474	0.197	**.016***
Total cholesterol (mg/dl)	-0.0003	0.001	.808
HDL- cholesterol (mg/dl)	-0.004	0.003	.197
Triglycerides (mg/dl)[a]	-0.039	0.100	.693
LDL- cholesterol (mg/dl)	0.0005	0.001	.695
BUN (mg/dl)	-0.005	0.009	.626
Creatinine (mg/dl)	-0.535	0.336	.112
Estimated GFR (ml/min/1.73m^2)[a]	-0.200	0.229	.383
Uric acid (mg/dl)	-0.046	0.038	.227
Hemoglobin A1c (%)	-0.0005	0.088	.995
Insulin (μU/ml)[a]	-0.051	0.070	.466
hs CRP (mg/dl)[a]	0.083	0.038	**.029****
sRAGE (ng/ml)[a]	-0.244	0.072	**.0008**
Smoking	0.189	0.182	.237
Alcohol	0.027	0.127	.834
Medications for			
Hypertension	-0.121	0.099	.225
Hyperlipidemia	-0.170	0.144	.240
Diabetes	-0.051	0.207	.807

Abbreviations: HMGB1, high mobility group box 1; HDL, high density lipoprotein; LDL, low density lipoprotein; BUN, blood urea nitrogen; GFR, glomerular filtration rate; hsCRP, high sensitive C reactive protein; sRAGE, soluble receptor for advanced glycation end products.
β indicates standardized regression coefficients: male = 0, female = 1.
[a] Log-transformed values were used for the analysis. *P <.05; **P <.001.

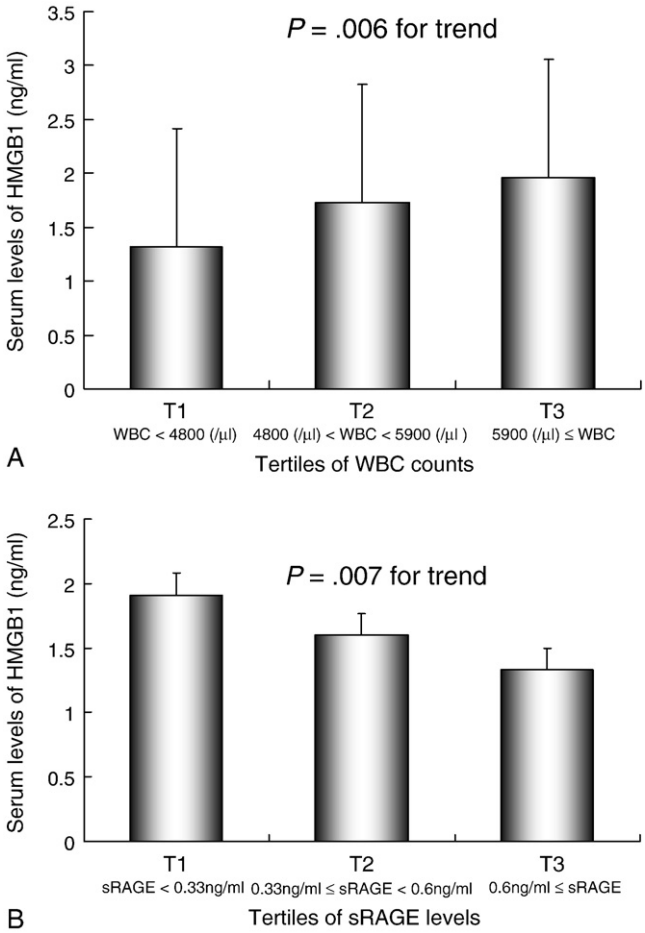

Fig. 2. Mean levels of HMGB1 stratified by tertiles of WBC counts (upper panel) and sRAGE (lower panel) adjusted for age and sex. ANCOVA was used for analysis. Log-transformed values were used for the analysis and reconverted to anti-logarithm forms for the serum levels of HMGB1.

correlated with renal function in patients with chronic kidney disease (CKD) in a small number of subjects [24]. The latter study found that, HMGB1 levels increase as the renal function deteriorates; HMGB1 levels in controls, CKD stage 3-4 and CKD stage 5 were 10.9 ± 10.5 ng/ml, 85.6 ± 31.8 ng/ml and 146.7 ± 58.9 ng/ml, respectively [24]. However, our present study , did not find any association between renal function (serum creatinine and estimated GFR) and serum HMGB1 levels. We do not know the reasons for this discrepancy, however differences in subject population (non-CKD vs. CKD) and ethnicity could be responsible. In their study, serum HMGB1 levels of healthy controls were one order of magnitude higher than those in our subjects. The use of different assay systems for the determination of serum HMGB1 (ELISA vs. western blot analysis) could explain this difference.

Table 3
Multiple stepwise regression analysis for correlates of serum HMGB1 levels

Characteristics	β	SE	*P*
sRAGE[a]	-0.247	0.072	.0007
WBC[a]	0.047	0.192	.016
			R^2 = 0.034

[a] Log-transformed values were used for the analysis.

The present study, found that WBC counts are independently correlated with HMGB1 levels. This various observation suggests that HMGB1 is a potential biomarker for subclinical inflammation. hsCRP is another well-known biomarker of inflammation. In this study, hsCRP was positively correlated with HMGB1 levels by multivariable analysis. However, hsCRP lost its significance by multiple stepwise regression analysis, possibly because of the close relationship between hsCRP and WBC counts. Our results may support the notion that WBCs release HMGB1 into the circulation [5]. However, our results don't indicate a causal relationship between WBC and HMGB1. Multiple stepwise regression analysis revealed that the R^2 (multiple regression coefficient) was only 0.034 and the P value for WBC counts was .016 (Table 3). Although we were not able to clarify the reasons for these low values, it may be due to the fact that we used WBC counts in our analysis instead of the monocytes that release HMGB1 into the circulation. There may well be determinants of serum HMGB1 levels other than WBC and sRAGE. Nevertheless, our results indicate that elevated

HMGB1 levels may be closely related to subclinical inflammation in apparently healthy subjects.

The present study, found that sRAGE levels were strongly and independently correlated with HMGB1 levels ($P < .001$, inversely). RAGE is thought to be one of the important receptors that mediate HMGB1 signaling [15-17]. RAGE promotes chemotaxis and maturation of immune cells, enhances the expression of adhesion molecules in endothelial cells, and stimulates the production of cytokines by various types of cells [17-19]. Moreover, sRAGE is absent and HMGB1 levels are higher in diabetic $RAGE^{-/-}/apoE^{-/-}$ mice, compared with diabetic $apoE^{-/-}$ mice [25]. Accordingly, we don't think the association of sRAGE and HMGB1 in the circulation could be an epiphenomenon. Rather, our results suggest that sRAGE may capture and eliminate circulating HMGB1. Consistent with this notion, previous observations suggest that circulating RAGE could protect tissues against pro-inflammatory reactions [21,26,27].

5. Limitations

First, although endogenous sRAGE could be generated from the cleavage of cell surface RAGE proteins or novel splice variants of RAGE [11], the assay used here does not distinguish the types of endogenous sRAGE. Second, our study was a cross-sectional one and therefore, does not elucidate the causal relationships between sRAGE levels or WBC counts and circulating HMGB1. Accordingly, we do not know how HMGB1 could be mechanistically related to inflammation and we cannot say for certain that sRAGE is able to capture and eliminate circulating HMGB1. A longitudinal study is needed to clarify the causal relationships among HMGB1, sRAGE levels, and inflammation. Third, although medications for diabetes, hypertension and hyperlipidemia were not correlated with circulating HMGB1 levels in our analyses, we were not able to exclude the contributions of some therapeutic agents because serum levels of sRAGE can be influenced by blockers of the renin-angiotensin system or by statins [28-31].

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